EXHIBIT Q

RLL-200US

#9A
11/20/02

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: CHANDRAN *et al.*

Examiner: Rebecca Cook

Application No.: 09/923,491

Group Art Unit: 1614

Filing Date: August 7, 2001

Title: LIQUID FORMULATION OF METFORMIN

Certificate of Mailing

I certify that this correspondence is being deposited on November 4, 2002 with the United States Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Box Non-Fee Amendment, Washington, D.C. 20231.

Christine Kenedy

Assistant Commissioner for Patents
Box Non-Fee Amendment
Washington, D.C. 20231

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Sir:

In response to the Office Action dated July 3, 2002, submitted herewith is a Petition for Extension of time, including the required fee, therefore, this response has been timely filed.

Also submitted are the following amendments:

In the Claims:

Please amend Claims 1, 8, 34, 35, 37, 39 to read as follows.

A1

1. A liquid pharmaceutical composition for oral administration to a subject in need thereof which comprises a therapeutically effective amount of metformin or its pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable liquid carrier.

A2 8. A liquid pharmaceutical composition which comprises a therapeutically effective amount of metformin, or its pharmaceutically acceptable salt, a sweetener that does not increase the blood glucose level of a subject after ingestion thereof, an alkyl hydroxyethylcellulose, a polyhydroxy alcohol, and a pharmaceutically acceptable carrier, said sweetener being present in amounts ranging from about 40% to about 80% by weight, said alkyl hydroxyethylcellulose being present in amounts ranging from about 0.01% to about 5% by weight and said polyhydroxy alcohol being present in amounts ranging from about 5% to about 55% by weight.

A3 27. The liquid pharmaceutical composition according to claim ~~22~~ or ~~23~~ which comprises a mineral acid and a bicarbonate salt both in sufficient amounts to maintain the pH in the range of about 4.0 to about 9.0.

A4 B 34. The liquid pharmaceutical composition according to ~~claim 1 or~~ claim ~~8~~ or ~~22~~ which additionally comprises ~~a further~~ another anti-hyperglycemic agent.

B 35. The liquid pharmaceutical composition according to claim ~~34~~, wherein the ~~further~~ other anti-hyperglycemic agent is glyburide or glypizide.

A5 B 37. The liquid pharmaceutical composition according to claim ~~4, 32 or~~ 36, additionally comprising ~~a further~~ another anti-hyperglycemic agent.

A6 B 39. The liquid pharmaceutical composition according to claim ~~38~~ which additionally comprises ~~a further~~ another anti-hyperglycemic agent.

REMARKS

Claims 1-50 are pending. Claims 1 and 8 have been amended to remove reference to "association," as suggested by the Examiner. Claim 27 has been amended, in light of amendments to other claims, to eliminate reference to "additionally comprising." Claims 34, 35, 37 and 39 have been amended to recite that a "further anti-hyperglycemic agent" be present. Claim 35 has also been amended to correct an erroneous dependency, formerly from claim 33, but now properly from claim 34. Support for these claim amendments is found in applicants' specification. Support for a "further anti-hyperglycemic agent" is found, for example, on page 16, lines 4-9. Support for the dependency of claim 35 from claim 34 is clear from inspection of the claims and the specification as a whole. No new matter is introduced by way of these amendments.

Objections to the Disclosure

The disclosure has been objected to because of an informality regarding page 19. Applicants submit herewith a correction to the disclosure on page 19, and respectfully request withdrawal of the objection.

The specification has further been objected to as failing to provide proper antecedent basis for method claims 42 and 43, as no support is seen in the text to support these claims. Applicants respectfully traverse the objection as follows.

Claim 42 recites a method for reducing adverse effects of metformin or its pharmaceutical salt when ingested, comprising administering a liquid pharmaceutical composition of claim 1, 8 or 22. The adverse effects of metformin and closely related materials (such as pharmaceutical salt) are disclosed by applicants, and are in any case well-known in the art. (see page 3, line 21 to page 4, line 3). The applicants' compositions are also described as potentially exhibiting fewer adverse effects than other metformin compositions. (see page 22, lines 16-19). Finally, it is quite clear that administration of applicants' compositions having these properties is disclosed. Thus, support is found for claim 42.

Claim 43 recites a method for facilitating compliance of a patient prescribed to take metformin or its pharmaceutically acceptable salt, comprising administering a liquid pharmaceutical composition of claim 1, 8 or 22. The issues of patient compliance with the administration of metformin compositions are disclosed by applicants, and are in any case well-known in the art. (see page 22, lines 8-15). The applicants' compositions are described as facilitating patient compliance with metformin administration directly in this cited section of the application. Thus, support for claim 43 is found.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-7, 33-35 and 37-43 have been rejected as indefinite. Applicants respectfully traverse the rejections for the following reasons.

Claim 1, and claims 2-7, 33, 38, 40-43 dependent therefrom, have been rejected as indefinite for reciting "in association with." The cited language has been removed in favor of language indicate by the Examiner as overcoming the rejection. It is thus believed that the rejection is thereby mooted.

Claims 34, 37, and 39, and claim 35 dependent therefrom, have been rejected as indefinite for the recitation "additionally comprises an anti-hyperglycemic agent," for compositions already comprising metformin. These claims have been amended to recite that the compositions "additionally comprise[s] a further anti-hyperglycemic agent in addition to metformin."

As expressed in the MPEP, § 2173.02, "The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. § 112, Second Paragraph is whether the claim meets the threshold requirements of clarity and precision " Also in this section of the MPEP, "Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." "In reviewing a claim for compliance with 35 U.S.C.§112, Second Paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. §112, Second Paragraph."

Claim 42 has been rejected as indefinite as it is allegedly not clear which adverse effects of metformin are reduced. As pointed out in applicants' specification, and as is well known in the art, "metformin hydrochloride salt has a pronounced saline bitter taste." (page 3, lines 21-22). The constraints on formulating acceptable compositions are discussed in applicants' specification (see, for example, page 4, lines 7-17). Thus, applicants submit that it would be clear to one of ordinary skill in the art what are the "adverse effects of metformin or its pharmaceutically acceptable salt" from the claim, from examination of the specification, and from common knowledge in the field. Thus, considering the application disclosure, the prior art teachings, and the claim interpretation of one of ordinary skill in the art, the scope and clarity of claim 42 is reasonably conveyed to one of ordinary skill in the art.

Claim 43 has been rejected as indefinite as it is allegedly not clear how the method facilitates compliance. As pointed out in applicants' specification, and as is well known in the art, a"liquid formulation is easy to swallow and administer." (page 22, line

12). Thus, applicants submit that it would be clear to one of ordinary skill in the art how "the method facilitates compliance" from the claim, from examination of the specification, and from common knowledge in the field. Consequently, one of ordinary skill in the art would have been reasonably apprised of the scope and clarity of claim 43.

Applicants respectfully request reconsideration and withdrawal of the rejections on these grounds.

Rejection Under 35 U.S.C. §103(a) Over WO 99/55320 to Sumitomo Pharmaceuticals Co., Ltd

Claims 1-50 have been rejected as obvious over Sumitomo. Applicants respectfully traverse the rejection for the following reasons.

Sumitomo discloses oral formulations including a biguanide and an organic acid. Metformin, buformin, and fenformin as the biguanide and malic, citric, and tartaric acid, or mixtures thereof as the organic acid are preferred (page 3, lines 7-9, and lines 12-14).

With respect to claim 7, the Examiner's position appears to be that Sumitomo's disclosure of "disintegrators such as carboxymethylcellulose calcium and low substituted hydroxy methyl celluloses" (page 4, lines 16-17) makes *prima facie* obvious applicants' use of alkyl hydroxyethylcellulose. The Examiner further asserts that "'320 discloses that other disintegrators may be used." In fact, applicants have been unable to locate such a statement or suggestion in Sumitomo. Applicants respectfully request that any continued rejection of the claims on these grounds be accompanied by citation to Sumitomo for this proposition.

In any case, these arguments cannot constitute a *prima facie* case of obviousness, since no cited combination of references contains all limitations of the rejected claims, and there is no cited motivation to modify the reference to arrive at applicants' claims. Further, recent case law strongly implies that an Examiner "cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies." In re Lee, 227 F.3d 1338 (Fed. Cir. 2002) (Board's reliance on "common knowledge and common sense" does not fulfill the agency's obligation to cite references to support its conclusions).

G

With respect to claims 8-39 and 44-50, it is to be noted that no cited prior art document discloses the use of an alkyl hydroxyethylcellulose and a polyhydroxy alcohol in the defined amounts for masking bitter taste of metformin in a liquid pharmaceutical composition. The Examiner appears to recognize this lack of disclosure in the cited references. Again, without motivation to modify a reference to arrive at applicants' claims, a *prima facie* case of obviousness cannot lie.

Also, with respect to claims 42 and 43, the Examiner's position is based on improper hindsight. Since these claims require compositions according to claims 1, 8 or 22, it cannot be simply said, as Examiner has done, that "it would be obvious to one of ordinary skill in the art that it would be easier to administer a pleasant tasting liquid formulation to a person not able to swallow a tablet than a bitter, salty liquid." This position clearly presupposes applicants' compositions, which is simply impermissible hindsight.

Applicants respectfully submit that the presently claimed invention is not obvious in light of Sumitomo, and request reconsideration and withdrawal of the rejection.

CONCLUSION

As all claims are believed to be presently allowable, applicants respectfully solicit a Notice of Allowance for the pending claims.

Respectfully submitted,
CHANDRAN et al.

By: _____
George E. Heibel, Ph.D.
Reg. No. 42,648

Dated: November 4, 2002
Ranbaxy Laboratories Limited
600 College Road East, Suite 2100
Princeton, New Jersey 08540
Tel: (609) 720-5608
Fax: (609) 514-9779

APPENDIX

1. A liquid pharmaceutical composition for oral administration to a subject in need thereof which comprises a therapeutically effective amount of metformin or its pharmaceutically acceptable salt thereof [in association with], and a pharmaceutically acceptable liquid carrier.

8. A liquid pharmaceutical composition which comprises a therapeutically effective amount of metformin, or its pharmaceutically acceptable salt, a sweetener that does not increase the blood glucose level of a subject after ingestion thereof, an alkyl hydroxyethylcellulose, [and] a polyhydroxy alcohol, [in association with] and a pharmaceutically acceptable carrier, said sweetener being present in amounts ranging from about 40% to about 80% by weight, said alkyl hydroxyethylcellulose being present in amounts ranging from about 0.01% to about 5% by weight and said polyhydroxy alcohol being present in amounts ranging from about 5% to about 55% by weight.

27. The liquid pharmaceutical composition according to claim 22 or 23 which [additionally] comprises a mineral acid and a bicarbonate salt both in sufficient amounts to maintain the pH in the range of about 4.0 to about 9.0.

34. The liquid pharmaceutical composition according to claim 1 or claim 8 or 22 which additionally comprises [an] a further anti-hyperglycemeic agent.

35. The liquid pharmaceutical composition according to claim [33] 34, wherein the further anti-hyperglycemic agent is glyburide or glypizide.

37. The liquid pharmaceutical composition according to claim 4, 32 or 36, additionally comprising [an] a further anti-hyperglycemic agent.

39. The liquid pharmaceutical composition according to claim 38 which additionally comprises [an] a further anti-hyperglycemic agent.